What is claimed is:

1. A method for producing hybridoma cells producing high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells, wherein said hybridoma cells express a dominant negative allele of a mismatch repair gene;

(c) incubating said parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen for binding of antibodies to antigen for antibodies produced from said hypermutated hybridoma cells; and

(e) selecting hypermutated hybridoma cells that produce antibodies with greater affinity for said antigen than antibodies produced by said parental hybridoma cells;

thereby producing hybridoma cells producing high-affinity antibodies.

2. The method of claim 1 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a gene selected from the group consisting of *PMS2*, *PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR* genes.

3. The method of claim 1 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

4. The method of claim 1 further comprising a screen for hypermutated hybridomas that also produce antibodies in higher titers than said parental hybridomas.

5. The method of claim 1 further comprising inactivation of said dominant negative allele of said mismatch repair gene, thereby stabilizing the genome of said hypermutated hybridoma.

6. The method of claim 4 further comprising inactivation of said dominant negative allele of said mismatch repair gene, thereby stabilizing the genome of said hypermutated hybridoma.

7. The method of claim 1 wherein said high affinity antibodies have an affinity of at least about 1 x 10^7 M^{-1} to about 1 x 10^{14} M^{-1}.

8. The method of claim 4 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

9. The method of claim 1 or 4 further comprising the step of inactivating said dominant negative allele of a mismatch repair gene by knocking out said dominant negative allele or removing an inducer of said dominant negative allele.

10. The method of claim 1 further comprising incubating said parental hybridoma cells with a chemical mutagen.

11. The method of claim 1 wherein the dominant negative mismatch repair gene is introduced into said hybridoma cell after the fusion of said myeloma with said immunoglobulin-producing cells.

12. The method of claim 1 wherein said myeloma cells express a dominant negative mismatch repair gene which is also expressed in said hybridoma cells.

13. A hybridoma cell producing high affinity antibodies produced by the method of claim 1, 4, 5, 6, 7, or 10.

14. An antibody produced by a hybridoma cell of claim 13.

15. A method for producing hybridoma cells that produce high titers of antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells, wherein said hybridoma cells express a dominant negative allele of a mismatch repair gene;

(c) incubating said parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen of said hypermutated hybridoma cells for antibodies produced in higher titers than that produced by said parental hybridoma cells; and

(e) selecting hypermutated hybridoma cells that produce higher titers of antibodies than that produced by said parental hybridoma cells;

thereby producing hybridoma cells that produce high titers of antibodies.

16. The method of claim 15 wherein said dominant negative allele of a mismatch repair gene is selected from the group consisting of a dominant negative allele of *PMS2*,*PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR*.

17. The method of claim 15 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

18. The method of claim 15 further comprising inactivation of said dominant negative allele of said mismatch repair gene, thereby stabilizing the genome of said hypermutated hybridoma.

19. The method of claim 15 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

20. The method of claim 18 wherein said dominant negative allele of a mismatch repair gene is inactivated by knocking out said dominant negative allele or removing an inducer of said dominant negative allele.

21. The method of claim 15 further comprising incubating said parental hybridoma cells with a chemical mutagen.

22. The method of claim 15 wherein the dominant negative mismatch repair gene is introduced into said hybridoma cell after the fusion of said myeloma with said immunoglobulin-producing cells.

23. The method of claim 15 wherein said myeloma cells express a dominant negative mismatch repair gene which is also expressed in said hybridoma cells.

24. A hybridoma cell producing high affinity antibodies produced by the method of claim 15, 18, or 21.

25. An antibody produced by a hybridoma cell of claim 24.

26. A recombinant myeloma cell comprising a polynucleotide sequence encoding a dominant negative mismatch repair protein.

27. The recombinant myeloma cell of claim 26 wherein said mismatch repair protein is selected from the group consisting of *PMS2*, *PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR* genes.

28. The recombinant myeloma cell of claim 26 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

29. The recombinant myeloma cell of claim 26 wherein said myeloma cell does not express immunoglobulin genes.

30. The recombinant myeloma cell of claim 29 wherein said myeloma cell is HAT sensitive.

31. The recombinant myeloma cell of claim 30 wherein said myeloma cell is EBV-negative.

32. A method for producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells;

(c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen;

(d) cloning immunoglobulin genes from said hybridoma into a mammalian expression cell, wherein said mammalian expression cell expresses a dominant negative allele of a mismatch repair gene;

(e) performing a screen for mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells; thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized human immunoglobulin-producing cells.

33. The method of claim 32 wherein said dominant negative allele of a mismatch repair gene is introduced into said mammalian expression cell prior to introduction of said immunoglobulin genes.

34. The method of claim 32 wherein said dominant negative allele of a mismatch repair gene is introduced into said mammalian expression cell after introduction of said immunoglobulin genes.

35. The method of claim 32 wherein said dominant negative allele of a mismatch repair gene is introduced into said mammalian expression cell simultaneously said immunoglobulin genes.

36. The method of claim 32 wherein said mismatch repair gene is selected from the group consisting of *PMS2*, *PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR* genes.

37. The method of claim 32 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

38. The method of claim 32 wherein said high affinity antibodies have an affinity of at least about 1×10^7 M^{-1} to about 1×10^{14} M^{-1}.

39. A mammalian expression cell produced by the method of claim 32.

40. An antibody produced by a mammalian expression cell of claim 39.

41. A method for producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells, wherein said hybridoma cells express a dominant negative allele of a mismatch repair gene;

(c) incubating said parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen for binding of antibodies to antigen for antibodies produced from said hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with greater affinity for said antigen than antibodies produced by said parental hybridoma cells;

(f) cloning immunoglobulin genes from said hybridoma into a mammalian expression cell;

thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells.

42. The method of claim 41 wherein said dominant negative allele of a mismatch repair gene is expressed in said myeloma cell and in said hybridoma cell.

43. The method of claim 41 wherein said dominant negative allele of a mismatch repair gene is introduced into said hybridoma cell after said fusion

44. The method of claim 41 wherein said mismatch repair gene is selected from the group consisting of *PMS2*, *PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR* genes.

45. The method of claim 41 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

46. The method of claim 41 wherein said high affinity antibodies have an affinity of at least about $1 \times 10^{7}\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$.

47. A mammalian expression cell produced by the method of claim 41.

48. An antibody produced by a mammalian expression cell of claim 47.

49. A method for producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells;

(c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen;

(d) cloning immunoglobulin genes from said hybridoma into a parental mammalian expression cell, wherein said mammalian expression cell expresses a dominant negative allele of a mismatch repair gene;

(e) incubating said parental mammalian expression cell to allow for mutagenesis, thereby forming hypermutated mammalian expression cells;

(f) performing a screen of hypermutable mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells; and

(g) performing a screen of hypermutable mammalian expression cells that secrete higher titers of antibodies than parental mammalian expression cells;

thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells.

50. The method of claim 49 wherein said dominant negative allele of a mismatch repair gene is introduced into said mammalian expression cell prior to introduction of said immunoglobulin genes.

51. The method of claim 49 wherein said dominant negative allele of a mismatch repair gene is introduced into said mammalian expression cell after introduction of said immunoglobulin genes.

52. The method of claim 49 wherein said dominant negative allele of a mismatch repair gene is introduced into said mammalian expression cell simultaneously said immunoglobulin genes.

53. The method of claim 49 wherein said mismatch repair gene is selected from the group consisting of *PMS2*, *PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR* genes.

54. The method of claim 49 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

55. The method of claim 49 wherein said high affinity antibodies have an affinity of at least about 1×10^7 M^{-1} to about 1×10^{14} M^{-1}.

56. The method of claim 49 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

57. Mammalian expression cells produced by the method of claim 49.

58. Antibodies produced by the mammalian expression cells ofclaim 57.

59. A recombinant, hypermutable mammalian expression cell comprising a polynucleotide sequence encoding a dominant negative mismatch repair protein.

60. The recombinant, hypermutable mammalian expression cell of claim 59 wherein said mismatch repair protein is selected from the group consisting of *PMS2*, *PMS1*, *PMSR3*, *PMSR2*, *PMSR6*, *MLH1*, *GTBP*, *MSH3*, *MSH2*, *MLH3*, or *MSH1*, and homologs of *PMSR* genes.

61. The recombinant, hypermutable mammalian expression cell of claim 59 wherein said dominant negative allele of a mismatch repair gene comprises a dominant negative allele of a *PMS2* gene.

62. A method for producing hybridoma cells producing high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells;

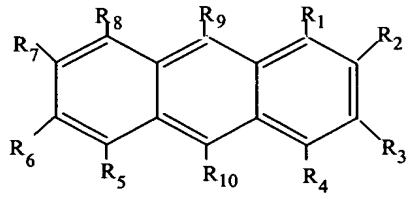
(d) performing a screen for binding of antibodies to antigen for antibodies produced from said hypermutated hybridoma cells; and

(e) selecting hypermutated hybridoma cells that produce antibodies with greater affinity for said antigen than antibodies produced by said parental hybridoma cells;

thereby producing hybridoma cells producing high-affinity antibodies.

63. The method of claim 62 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

64. The method of claim 62 wherein said inhibitor is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

65. The method of claim 64 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

66. The method of claim 62 further comprising a screen for hypermutated hybridomas that also produce antibodies in higher titers than said parental hybridomas.

67. The method of claim 62 further comprising the step of removing said chemical inhibitor from said growth medium following hypermutation, thereby stabilizing the genome of said hypermutated hybridoma.

68. The method of claim 66 further comprising the step of removing said chemical inhibitor from said growth medium following hypermutation, thereby stabilizing the genome of said hypermutated hybridoma.

69. The method of claim 62 wherein said high affinity antibodies have an affinity of at least about 1×10^7 M^{-1} to about 1×10^{14} M^{-1}.

70. The method of claim 66 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

71. A hybridoma cell produced by the method of claim 62, 66, 67, or 68.

72. An antibody produced by a hybridoma cell of claim 71.

73. A method for producing hybridoma cells that produce high titers of antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells;

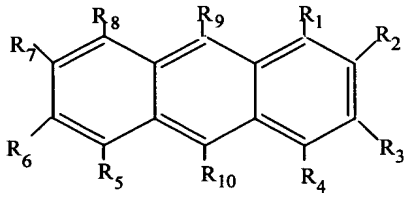
(d) performing a screen of said hypermutated hybridoma cells for antigen-specific antibodies produced in higher titers than that produced by said parental hybridoma cells; and

(e) selecting hypermutated hybridoma cells that produce higher titers of antibodies than that produced by said parental hybridoma cells;

thereby producing hybridoma cells that produce high titers of antibodies.

74. The method of claim 73 wherein said chemical inhibitor is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

75. The method of claim 74 wherein said inhibitor is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

76. The method of claim 75 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

77. The method of claim 73 further comprising the step of removing said chemical inhibitor from said growth medium following hypermutation, thereby stabilizing the genome of said hypermutated hybridoma.

78. The method of claim 73 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

79. A hybridoma cell produced by the method of claim 73 or 77.

80. An antibody produced by a hybridoma of claim 79.

81. A method for producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells;

(c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen;

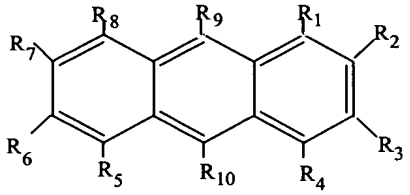
(d) cloning immunoglobulin genes from said hybridoma into a mammalian expression cell;

(e) incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair;

(f) performing a screen for mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells; thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells.

82. The method of claim 81 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

83. The method of claim 82 wherein said inhibitor is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

84. The method of claim 83 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

85. The method of claim 81 further comprising screen, prior to collection of said antibodies from said hypermutated hybridoma cells, for hypermutated hybridomas that also produce antibodies in higher titers than said parental hybridomas.

86. The method of claim 81 wherein said high affinity antibodies have an affinity of at least about 1×10^7 M^{-1} to about 1×10^{14} M^{-1}.

87. The method of claim 81 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

88. The method of claim 81 further comprising removing said chemical inhibitor, thereby stabilizing the genome of said hypermutated mammalian expression cells.

89. A mammalian expression cell produced by the method of claim 81, 85, or 88.

90. An antibody produced by a mammalian expression cell of claim 89.

91. A method for producing mammalian expression cells that produce high titers of high affinity antibodies to a selected antigen from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells;

(c) incubating said hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells;

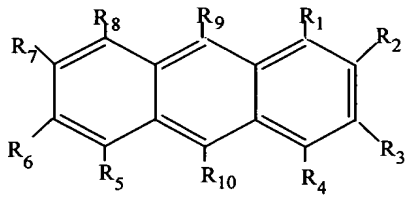
(d) performing a screen for binding of antigen for antibodies produced from said hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with greater affinity for said antigen than antibodies produced by said parental hybridoma cells;

(f) cloning immunoglobulin genes from said hypermutated hybridoma cells into a mammalian expression cell, thereby forming parental mammalian expression cells; thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells.

92. The method of claim 91 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

93. The method of claim 91 wherein said inhibitor is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

94. The method of claim 92 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

95. The method of claim 91 wherein said high affinity antibodies have an affinity of at least about 1×10^7 M^{-1} to about 1×10^{14} M^{-1}.

96. The method of claim 91 further comprising the steps of:

incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair, thereby forming a hypermutated mammalian expression cell; and

screening for hypermutated mammalian expression cells that produce a higher titer of antibodies that said parental mammalian expression cells.

97. The method of claim 91 further comprising removing said chemical inhibitor, thereby stabilizing the genome of said hypermutated hybridoma cells.

98. The method of claim 96 further comprising removing said chemical inhibitor, thereby stabilizing the genome of said hypermutated mammalian expression cells.

99. The method of claim 96 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

100. A mammalian expression cell produced by the method of claim 91, 95, 96, or 97.

101. An antibody produced by a mammalian expression cell of claim 100.

102. A method for producing hybridoma cells that produce high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells in high titers comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*, wherein said donor cells are derived from a donor that is naturally deficient in mismatch repair;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells, wherein said parental hybridoma cells are deficient in mismatch repair;

(c) incubating the said parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen for binding of antibodies to antigen for antibodies produced from said hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with enhanced affinity for the antigen than antibodies produced by said parental hybridoma cells;

(f) performing a second screen for hypermutated hybridoma cells that produce increased titers of antibodies as compared with said parental hybridoma cells;

(g) selecting hypermutated hybridoma cells that produce antibodies in higher titers than produced by said parental hybridoma cells;

thereby producing hybridoma cells producing high titers of high-affinity antibodies.

103. The method of claim 102 further comprising the step of introducing a wild-type gene for mismatch repair into said selected hypermutated hybridoma cell to complement the mismatch repair deficiency, thereby restabilizing the genome of said selected hypermutated hybridoma cell.

104. The method of claim 102 further comprising incubating said parental hybridoma cells with a chemical mutagen.

105. A hybridoma cell produced by the method of claim 102, 103, or 104.

106. An antibody produced by a hybridoma cell of claim 105.

107. A method for producing hybridoma cells that produce high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells in high titers comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells, wherein the myeloma cells are naturally deficient in mismatch repair, thereby forming parental hybridoma cells, wherein the hybridoma cells are deficient in mismatch repair;

(c) incubating said parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen for binding of antibodies to antigen for antibodies produced from said hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with enhanced affinity for the antigen than antibodies produced by said parental hybridoma cells;

(f) performing a second screen for hypermutated hybridoma cells that produce increased titers of antibodies as compared with parental hybridoma cells;

(g) selecting hypermutated hybridoma cells that produce antibodies in higher titers than produced by said parental hybridoma cells;

thereby producing hybridoma cells producing high titers of high-affinity antibodies.

108. The method of claim 107 further comprising introducing a wild-type gene for mismatch repair into said selected hypermutated hybridoma cell to complement the mismatch repair deficiency, thereby restabilizing the genome of said selected hypermutated hybridoma cell.

109. The method of claim 107 further comprising incubating said parental hybridoma cells with a chemical mutagen.

110. The method of claim 107 wherein said high affinity antibodies have an affinity of at least about $1 \times 10^{7}\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$.

111. The method of claim 107 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

112. A hybridoma cell produced by the method of claim 107, 108, or 109.

113. An antibody produced by a hybridoma cell of claim 112.

114. A method for producing mammalian expression cells that produce high-affinity antibodies in high titers from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*, wherein the donor cells are derived from a donor that is naturally deficient in mismatch repair;

(b) fusing the immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells, wherein the hybridoma cells are deficient in mismatch repair;

(c) incubating the parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen for binding of antibodies to antigen for antibodies produced from the hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with enhanced affinity for the antigen than antibodies produced by the parental hybridoma cells;

(f) cloning immunoglobulin genes from said hypermutated hybridoma into a mammalian expression cell;

thereby producing a mammalian expression cell that produce high titers of high-affinity antibodies in high titer from *in vitro* immunized immunoglobulin-producing cells.

115. The method of claim 114 wherein said high affinity antibodies have an affinity of at least about $1 \times 10^{7}\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$.

116. The method of claim 114 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

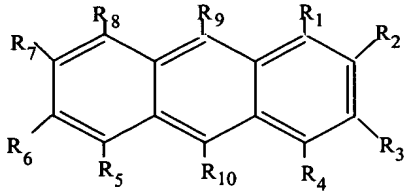
117. The method of claim 114 further comprising the steps of:

incubating the mammalian expression cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells; and

screening said hypermutated mammalian expression cells for higher production of antibodies than that of the parental mammalian expression cells.

118. The method of claim 117 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

119. The method of claim 117 wherein said inhibitor is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

120. The method of claim 119 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

121. The method of claim 117 further comprising the step of removing said chemical inhibitor of mismatch repair from the hypermutated mammalian expression cells, thereby stabilizing the genome of said hypermutated mammalian expression cells.

122. A mammalian expression cell produced by the method of claim 114, 117, 118, or 121.

123. An antibody produced by a mammalian expression cell of claim 122.

124. A method for producing mammalian expression cells that produce high-affinity antibodies in high titer from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing the immunoglobulin-producing cells with myeloma cells, wherein the myeloma cells are naturally deficient in mismatch repair, thereby forming parental hybridoma cells, wherein the hybridoma cells are deficient in mismatch repair;

(c) incubating the parental hybridoma cells to allow for mutagenesis, thereby forming hypermutated hybridoma cells;

(d) performing a screen for binding of antibodies to antigen for antibodies produced from the hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with enhanced affinity for the antigen than antibodies produced by the parental hybridoma cells; and

(f) cloning immunoglobulin genes from said hypermutated hybridoma cell into a mammalian expression cell;

thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from *in vitro* immunized immunoglobulin-producing cells.

125. The method of claim 124 wherein said high affinity antibodies have an affinity of at least about 1×10^{7} M^{-1} to about 1×10^{14} M^{-1}.

126. The method of claim 124 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

127. The method of claim 124 further comprising the steps of:

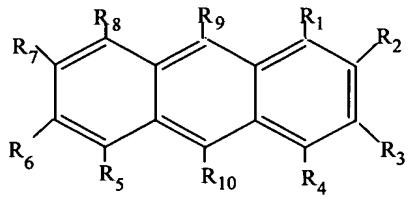
incubating the mammalian expression cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells; and

screening said hypermutated mammalian expression cells for higher production of antibodies than that of the parental mammalian expression cells.

128. The method of claim 127 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an

RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

129. The method of claim 127 wherein said inhibitor is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

130. The method of claim 129 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

131. The method of claim 127 further comprising the step of removing said chemical inhibitor of mismatch repair from the hypermutated mammalian expression cells, thereby stabilizing the genome of said hypermutated mammalian expression cells.

132. A mammalian expression cell produced by the method of claim 124, 127, or 131.

133. An antibody produced by a mammalian expression cell of claim 132.

134. A method for *in vitro* production of antigen-specific immunoglobulin-producing cells comprising:

(a) isolating donor cells from an animal;

(b) treating said cells with L-leucyl-L-leucine methy ester hydrobromide;

(c) incubating said donor cells with an immunogenic antigen *in vitro*, at 25-37°C, 5-10% CO_2, in medium supplemented with 5-15% serum, and a growth promoting cytokine for 4 days;

(d) washing said cells in medium; and

(e) culturing said cells in medium supplemented with 5-15% serum an additional 8 days;

thereby stimulating the production of antigen-specific immunoglobulin-producing cells.

135. The method of claim 62, 73, 81, 91, 117, or 127 wherein said chemical inhibitor of mismatch repair is an antisense molecule comprising at least 15 consecutive nucleotides of a sequence encoding a protein selected from the group consisting of SEQ ID NO:2; SEQ ID NO:4; SEQ ID NO:6; SEQ ID NO:8; SEQ ID NO:10; SEQ ID NO:12; SEQ ID NO:14; SEQ ID NO:16; SEQ ID NO:18; SEQ ID NO:20; SEQ ID NO:22; SEQ ID NO:24; SEQ ID NO:26; SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:32; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:38; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:44; SEQ ID NO:46; SEQ ID NO:48; and SEQ ID NO:50.

136. The method of claim 62, 73, 81, 91, 117, or 127 wherein said chemical inhibitor of mismatch repair is an antisense molecule comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; SEQ ID NO:21; SEQ ID NO:23; SEQ ID NO:25; SEQ ID NO:27;

SEQ ID NO:29; SEQ ID NO:31; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:37; SEQ ID NO:39; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:45; SEQ ID NO:47; and SEQ ID NO:49.

137. A hybridoma cell producing high affinity antibodies produced by the method of claim 9.

138. An antibody produced by a hybridoma cell of claim 137.